Applicants' file reflects the submission of a PTO-1449 and it is regretted if the Examiner's copy of the papers omits such documentation.

Submitted with the confirmation copy of this facsimile transmission is a PTO-1449 with respect to the prior art referred to in the specification and cited in related applications. Copies of the cited references are also enclosed with that copy. The enclosed deposit account form includes the prescribed fee for the filing of a PTO-1449 at this stage.

The Examiner objected to the drawings, since each Figure must be labelled. The Examiner noted that Figures 6, 9 and 10 comprise two or more views which must be labelled separately. It is noted that the Preliminary Amendment labelled the separate views as panels. The Brief Description of the Drawings on page 10 has been further amended to use discrete Figure labels. In addition, it is proposed to amend Figures 6, 9 and 10, as shown on the enclosed print in red, in order to be consistent with this labelling.

The Examiner objected to the Abstract of the Disclosure as being in the form of two paragraphs. A new Abstract is enclosed in which there is a single paragraph.

The Examiner noted that applicants' specification refers to the old address of ATTC. The specification has been amended in this regard to use the current address.

The Examiner noted use of certain trademarks in the application. The Examiner indicated that all such trademarks should be capitalized and be accompanied be generic terminology. The terms used have be acknowledged as trademarks and capitalized. Generic terminology already exists in the description of their function.

The Examiner rejected claims 1 to 11, 27 and 28 under 35 USC 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In this regard the Examiner raised a number of issues, discussed separately below:

(a) The Examiner considered claims 1 and 27 indefinite on the basis that it is unclear whether the antigen presenting cells are genetically modified

or whether the antibody conjugate molecule is genetically modified. In this regard, claims 1 and 27 have been amended to clarify that it is the monoclonal antibody which is genetically modified.

(b) The Examiner considers that claims 27 and 28 read on a compound, since no additional components are mentioned. In this regard, claim 27 has been amended to recite the essential purpose of a pharmaceutically-acceptable carrier. It is submitted that sufficient basis for such recitation appears in the specification, such as the discussion on vaccine preparation and use on pages 16 and 17 of the specification.

(c) The Examiner considered the phrase "exclusively at at least one" to be indefinite on the basis that it is unclear how the claimed product could be exclusive. The term "exclusive" is intended to refer to the fact that the antigen is located at a specific pre-selected site only on the monoclonal antibody moiety. If the monoclonal antibody moiety is genetically modified to contain more than one antigen, then such additional antigen also is located at a specific pre-selected site only on the monoclonal antibody moiety. In this regard, the language of claims 1 and 27 has been modified to specify that each antigen is located exclusively at a pre-selected site on the monoclonal antibody.

(d) The Examiner considered the term "weakly", as used in claim 7, to be a relative term. The term is used in claim 7 in connection with the antigen being an inherently weakly-immunogenic antigen moiety. While there may be some relativity in the term employed, it is submitted that the term is a term of the art of immunology and, in this regard, it is noted that the term is used, for example, in claim 3 of U.S. Patent No. 5,494,254, cited by the Examiner.

(e) The Examiner noted that claims 2 to 11 refer to the term "molecule". The Examiner suggested that the term be modified to recite "a

recombinant conjugate antibody molecule". The Examiners' suggestion in this regard has been adopted.

(f) The Examiner indicated that the term "wherein said at least one antigen moiety comprises a plurality of antigen moieties", used in claim 8, was unclear. The language of the claim has been amended to specify that the monoclonal antibody moiety is modified to contain a plurality of antigen moieties.

Having regard to the changes made to the claim and the above discussion, it is submitted that claims 1 to 11, 27 and 28 can no longer be considered indefinite and hence the rejection thereof under 35 USC 112, second paragraph, should be withdrawn.

The Examiner rejected claims 1, 2, 27 and 28 under 35 USC 102(b) as being anticipated by Barber (U.S. Patent No. 4,950,480). The Examiner also rejected claims 1, 27 and 28 under 35 USC 102(b) as being anticipated by Barber (U.S. Patent No. 5,194,254).

The two Barber patents contain essentially the same description. These references disclose the provision of anti-class II monoclonal antibodies coupled to antigens to target class II bearing antigen-presenting cells to bring about engagement of both the B and T cell components of an immune response. This brings about an enhancement of the immunotargeting of the antigen, in the absence of conventional adjuvants.

In this system, biotin-strepthuidin based interaction was used to bind the antibody and antigen. However, as specified in the disclosure, there are inherent disadvantages with such chemical coupling techniques, such as yield (about 20%) and also the variability factor between different preparations. In such procedures there is no adequate control on the amounts of coupled peptides as well as the exact location of the reaction.

By way of contrast, the applicants' employ a recombinant approach and provide a recombinant conjugate antibody molecule. By using the recombinant approach, the difficulties of the biotin- strepthuidin based interactions are overcome. In the present invention, each antigen moiety contained within the monoclonal

antibody moiety in the recombinant conjugate antibody molecule is located exclusively at a preselected.

Since such structure is not possible with the procedures described in the Barber patents, it is submitted that none of applicants' claims can be anticipated by the Barber references and hence the rejection of claims 1, 2, 27 and 28 under 35 USC 102(b) as being anticipated by Barber (U.S. Patent 4,950,480) and the rejection of claims 1, 2, 27 and 28 under 35 USC 102(b) as being anticipated by Barber (U.S. Patent No. 5,194,254) should be withdrawn.

The Examiner rejected claims 1 to 11 and 27 to 28 under 35 USC 102(a) as being anticipated by Baier et al.

It is noted that the rejection properly is made under 35 USC 102(a), since the reference was published less than one year prior to applicants' effective filing date. Applicants' have evidence which permits them to swear back of the Baier et al reference, showing construction of the expression plasmid pCMV dhfr.chICHC, expression of chimeric 44H104-CCTB36 conjugate and immunization of macaques with the conjugate, well before the publication date of the Baier et al reference. Applicants' are willing to submit evidence in the form of a Declaration under 38 CFR 1.131 in the event the Examiner is not persuaded that the claims are not anticipated by Baier et al.

Applicants' claims are directed to recombinant conjugate antibody molecule consisting of a bivalent monoclonal antibody moiety having heavy and light chains. At the Interview, the Examiner indicated that she was not satisfied that this language excluded fragments. It is submitted that the language clearly indicates that the whole antibody molecule is employed. For greater certainty, claims 1 and 27 have been further amended to specify that the monoclonal antibody molecule has its entire heavy and light chains.

The Baier reference states:

> "... chimeric anti-human HLA-DR or sIgD antibodies incorporating an immunodominant V3 loop peptide, P18, and a potent Th epitope, EnvT1 (T1), both derived from the gp120 envelope glycoprotein of HIV-1_{IIIB}, were expressed in *Escherichia coli* and purified as <u>monovalent Fab fragments</u>."

The authors then determined that the chimeric Fabs bound specifically to human

APCs displaying the relevant HLA-DR sIgD molecules and demonstrated improved immunogenicity as measured by increased stimulation of IL-2 production *in vitro* by human $CD4^+$ Th cells from donors exposed to HIV-1 antigens.

The work reported by Baier et al, therefore, is entirely concerned with monovalent Fab fragments and has nothing to do with the use of whole monoclonal antibody, as in the case of applicants. The Examiner remarks in the Office Action that:

> "Baier teaches bivalent monoclonal antibodies . . . (see page 2363, col. 2, paragraph 2)."

This passage is found in the discussion part of the Baier et al paper. Baier indicates that several potential limitations of the immunotargeting vaccine approach described by Baier et al need to be addressed. The authors then observed (in the passage referred to by the Examiner):

> ". . . bivalent immunotargeting (anti-sIg) $F(ab')_2$ fragments were found to be ~10-fold more potent than the respect molovalent Fab fragments in enhancing T-cell activation" (emphasis added).

This passage, therefore, compares monovalent and bivalent antibody fragments.

As already noted, the applicants' invention utilizes the complete monoclonal antibody. Accordingly, it is submitted that claims 1 to 11 and 27 to 28 are not anticipated by Baier et al, and hence the rejection thereof under 35 USC 102(a) as being anticipated by this prior art, should be withdrawn.

The Examiner rejected claims 1 to 4, 27 and 28 under 35 USC 102(a) as being unpatentable over Barber (U.S. Patent No. 4,950,480) in view of Skea. The Examiner rejected claims 1 to 4, 27 and 28 under 35 USC 102(a) as being unpatentable over Barber (U.S. Patent No. 5,194,254) in view of Skea. As noted previously, the disclosures of the two Barber references are equivalent.

The distinction of the present invention, as defined in the claims, over the Barber references has been discussed in detail above. It is submitted that the Skea reference does not remedy the basic defects of the Barber references. In particular, the Skea et al reference uses the same avidin-biotin conjugation method as disclosed by Barber (note that Barber is a co-author on the Skea et al paper). Since this reference employs the same conjugation procedure as Barber, it suffers

from the same defects and cannot remedy those of Barber.

Accordingly, it is submitted that claims 1 to 4, 27 and 28 are patentable over the applied prior art and hence the rejection thereof under 35 USC 103(a) as being unpatentable over Barber (U.S. Patent No. 4,950,480) and Barber (U.S. Patent No. 5,194,254) in view of Skea, should be withdrawn.

The Examiner rejected claims 1 to 11, 27 and 28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 12 of U.S. Patent No. 4,950,480. The Examiner also rejected claims 1 to 11, 27 and 28 under judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 12 of U.S. Patent No. 5,194,254.

It is submitted that the claims of this application define structurally and patentably over the claims of the granted patent. It is submitted that there is no suggestion from the claimed subject matter of the Baeir patents to provide applicants' claimed recombinant conjugate antibody molecule as claimed.

Accordingly, it is submitted that claims 1 to 11, 27 and 28 are patentably distinguished from claims 1 to 13 of U.S. Patent No. 4,950,480 and from claims 1 to 12 of U.S. Patent No. 5,194,254 and hence the rejections thereof under the judicially created doctrine of obviousness-type double patenting over the claims of Barber (U.S. Patent No. 4,950,480) or Barber (U.S. Patent No. 5,194,254), should be withdrawn.

It is believed that this application now is in condition for allowance and early and favorable consideration and allowance are respectfully submitted.

Respectfully submitted,

Michael I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada
(416) 595-1155
FAX No. (416) 595-1163

09/007093

ABSTRACT OF THE DISCLOSURE

Antibody molecules specific for surface structures of antigen presenting cells that have been modified to include an antigen moiety at a specific site therein to produce novel conjugate antibody molecules are disclosed. These conjugate molecules are produced by genetic modification of genes encoding light and heavy chains of the surface structure specific antibody, and expression in mammalian cells to produce the conjugate antibody. The conjugate antibody retained specificity for antigen presenting cells and contained the antigen moiety. The conjugate antibody molecules deliver the antigen to antigen presenting cells to produce an enhanced immune response to a host immunized therewith. The conjugate antibody molecules and nucleic acid molecules encoding them are useful as antigens and as immunogens in diagnostic and prophylactic applications.